EXHIBIT A

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

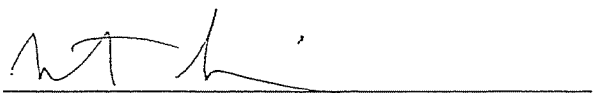
SMITH KLINE & FRENCH LABORATORIES, LTD, AND SMITHKLINE BEECHAM CORP., d/b/a GLAXOSMITHKLINE, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 05-197 GMS

DEFENDANT TEVA PHARMACEUTICALS' CORRECTED MOTION FOR LEAVE TO AMEND ITS ANSWER, DEFENSES, AND COUNTERCLAIMS

Defendant Teva Pharmaceuticals U.S.A., Inc. ("Teva") moves, pursuant to Federal Rule of Civil Procedure 15(a), for leave to amend its Answer, Defenses, and Counterclaims to add affirmative defenses and declaratory judgment counterclaims stemming from Plaintiffs' inequitable conduct in obtaining U.S. Patent Nos. 4,452,808 and 4,824,860, which Plaintiffs allege Teva has infringed. As discussed in detail in the accompanying memorandum (filed under seal), this Court should permit Teva to amend its answer to add these defenses and counterclaims even though the deadline for amending pleadings set in the Court's original Scheduling Order has elapsed. Teva only recently discovered the evidence needed to plead these allegations with particularity as required under the Federal Rules. Moreover, Teva's addition of these defenses and counterclaims is not brought for an improper purpose and would not be futile. Nor would Teva's amendment of its answer unduly prejudice Plaintiffs, and Teva does not believe that the proposed amendment should affect the Court's previously scheduled trial date.

Prior to filing this motion, Teva made reasonable efforts to seek Plaintiffs' agreement not to oppose Teva's filing of its amended answer, including by sending a copy of Teva's proposed amended answer to opposing counsel by letter dated June 21, 2006. On June 23, 2006, Teva was informed that Plaintiffs would oppose Teva's efforts to amend its answer. Accordingly, Teva files the instant motion seeking leave from the Court to file its amended answer with the expectation that Plaintiffs will oppose Teva's motion.

Respectfully submitted,



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Dated: July 10, 2006

EXHIBIT B

United States Patent [19]

Gallagher, Jr.

[11] **4,452,808**

[45] **Jun. 5, 1984**

[54] **4-AMINOALKYL-2(3H)-INDOLONES**

[75] Inventor: Gregory Gallagher, Jr., Collegeville, Pa.

[73] Assignee: Smithkline Beckman Corporation, Philadelphia, Pa.

[21] Appl. No.: 447,564

[22] Filed: Dec. 7, 1982

[51] Int. Cl.³ C07D 209/32; A61K 31/40

[52] U.S. Cl. 424/274; 548/486

[58] Field of Search 548/486; 424/274

[56] References Cited

U.S. PATENT DOCUMENTS

3,573,310 3/1971 Van Dyke 548/486

4,317,944 2/1982 Huffman et al.

FOREIGN PATENT DOCUMENTS

895875 3/1972 Canada 548/486

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[57] ABSTRACT

A series of new chemical compounds which are 4-aminoalkyl-2(3H)-indolones has been demonstrated to be D_2-agonists useful for treating hypertension. A representative compound of the series is 4-di-n-propylaminoethyl-2(3H)-indolone.

12 Claims, No Drawings

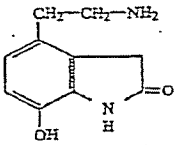
4-AMINOALKYL-2(3H)-INDOLONES

This invention relates to certain novel 4-aminoalkyl-2(3H)-indolones as well as to anti-hypertensive compositions and methods which use them.

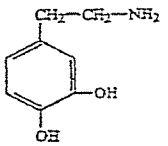
BACKGROUND OF THE INVENTION

4-Aminoalkyl-7-hydroxy-2(3H)-indolones are described in U.S. Pat. No. 4,314,944 to have a beneficial effect on abnormal conditions of the cardiovascular system. More specifically, such compounds are said to have a vasodilatation effect on the kidney which is similar to that of dopamine, thereby inducing anti-hypertensive activity due to a dopaminergic mechanism.

The basic structure of the prior art compounds is similar to that of the well known cardiovascular agent they mimic, dopamine:



U.S. Pat. No. 4,314,944



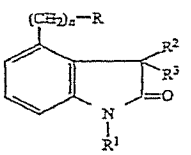
Dopamine

One skilled in the structure function art will appreciate that the 7-hydroxy group of the compounds of the prior art is necessary for them to resemble the structure of dopamine. Without this key group, the resulting compounds would not be expected to have cardiovascular activity.

DESCRIPTION OF THE INVENTION

The indolone compounds of this invention have beneficial cardiovascular activity despite the lack of the supposedly essential 7-hydroxy group. In addition to not having a catechol or catechol-mimicking structure, these indolones may not be subject to tachyphylaxis and are better absorbed orally when compared with the prior art compounds based on preliminary pharmacological tests with the preferred species of this invention.

The compounds are illustrated by the following structural formula:



in which:

R is amino, lower alkylamino, di-lower alkylamino, allylamino, diallylamino, N-lower alkyl-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethylamino or di-(4-hydroxyphenethylamino);

R^1, R^2 or R^3 are, each, hydrogen or lower alkyl; and

n is 1–3.

A subgeneric group of this invention comprises the compounds of formula I in which:

R is amino, di-n-propylamino, n-propyl-n-butylamino or 4-hydroxyphenethylamino;

R^1, R^2 or R^3 are hydrogen; and

$(CH_2)_n$ is ethylene ($—CH_2—CH_2—$).

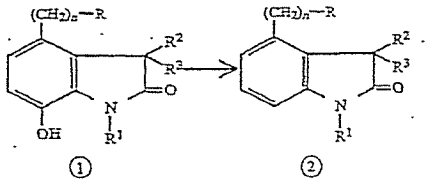
A preferred species of this invention is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or one of its pharmaceutically acceptable, acid addition salts.

The term "lower alkyl" used herein and in the claims is meant, for convenience, to include branched and straight chain groups of from 1–6 carbons, preferably n-propyl, for each alkyl in R and from 1–4 carbons, preferably methyl, for each of R^1, R^2 and R^3. R^1, R^2 and R^3 are preferably, for ease of preparation, all the same.

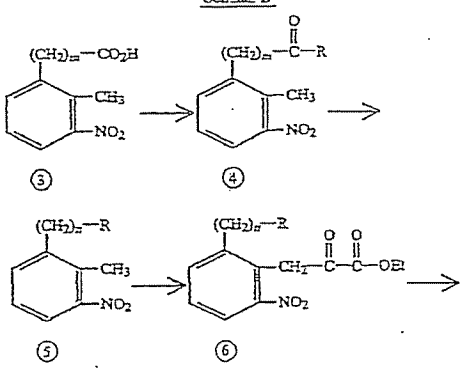
The pharmaceutically acceptable acid addition salts having the utility of the free bases of formula I are part of this invention. These are prepared by methods well known to the art and are formed with both inorganic or organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methane sulfonic, ethane disulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids. The hydrohalic and, especially, methane sulfonic acid salts are conveniently used.

The compounds of this invention are prepared by the following reaction sequences:

Scheme A



Scheme B



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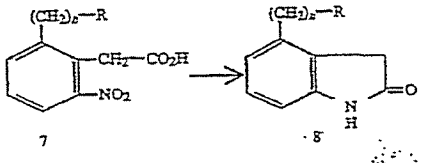

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In the reaction sequences of Schemes A and B above, n, R, R^1, R^2 and R^3 are as described for formula I; m is n—1. In some cases, such as where R is a primary or secondary amino, a protective group may be present, as described in more detail below.

In addition to the reaction sequences noted above, the compounds of this invention are prepared by the reactions which are described in U.S. Pat. No. 4,314,944, using, of course, known deshydroxy or desmethoxy starting materials. In preparing the present 7-unsubstituted indolones by this route, the ring closure to form the isatin ring at column 2 of that patent can proceed to give two isomeric products which must then be separated to yield the indolones of this invention.

In Scheme A, the corresponding 7-hydroxy indolone starting material (1) is de-hydroxylated by reacting it with at least a stoichiometric quantity of a reactive 5-halo-1-phenyl-1H-tetrazole in the presence of an acid binding agent, such as an alkali metal carbonate, in a suitable inert solvent, such as aqueous acetone, dimethylformamide or dimethylacetamide. The reaction is carried out at room temperature until substantially complete. From one to two days may be used. If desired, the reaction may be carried out in shorter time by operating at a higher temperature, for example, up to 75°.

The resulting new intermediate, a 4-(aminoalkyl)-7-(1-phenyl-1H-tetrazazol-5-yloxy)-2(3H)-indolone, is subjected to hydrogenation to split the tetrazole-oxyindolone link. Conveniently, catalytic hydrogenation, for example using a noble metal catalyst at moderate pressures of hydrogen and some heat, such as palladium-on-charcoal at 50° for 20 hours under 55 p.s.i., is used.

When R is a reactive amino, the starting material (1) is used in the form of an acid addition salt or an otherwise amino protected derivative. If a hydrogenation labile protective group is present on compound 1, it is also split during the reduction.

The reactions of Sequence B involve the insertion of the aminoalkyl side chain into the phenyl ring (1→7) followed by ring closure of the o-carboxymethyl-m-nitro intermediate (7). The ring closure is carried out by reduction of the intermediate, for example, using catalytic hydrogenation over a noble metal, preferably palladium, catalyst in a suitable solvent, for example, a lower alcohol, dilute hydrochloric acid or glacial acetic acid, at moderate pressures of hydrogen and at a temperature chosen from the range of room temperature to 60°. The reaction proceeds quickly to completion. The nitro group of compound 7 is reduced first, followed by ring closure.

As noted above, this reaction sequence is adaptable to prepare the compounds having a reactive aminoalkyl side chain by protecting an amine or another reactive group with a standard protecting means such as forming a maleimide, tert. boc or phthalimide derivative, which is removed, by standard reactions, after ring closure. The phthalimido-protective group, for example, is split using reaction with hydrazine hydrate. A benzyloxy is split by using catalytic hydrogenation; a tert.-boc, using mild acid.

The alkylated products of this invention are, alternatively, or, in certain instances, preferentially prepared by alkylation of the parent amino compounds of formula I in which R is amino or a secondary amino. For example, the N-alkylated products, formula I when R is a secondary or tertiary amino, are conveniently prepared by reductive alkylation using, for example, the aldehyde in one or two molar equivalent quantities under reduction conditions, such as under catalytic hydrogenation conditions over a palladium or platinum catalyst or such as using formaldehyde-formic acid when R is dimethylamino.

N-Alkylation, such as using an allyl or benzyl halide in the presence of an acid binding agent, can be used under standard mild conditions. Protecting the amido hydrogen in the ring is also used during alkylation if necessary as known to the art. Alkyl substituents at the 1 or 3-positions of the indolone ring are introduced by forming the lithio derivatives at the ring position, such as using butyl lithium, followed by reaction with a lower alkyl halide, especially an alkyl iodide. This process is similar to that reported by A. S. Kende et al., Syn. Commun. 12 1 (1982).

The compounds of this invention have utility, as specific dopamine agonists, in the treatment of disorders of the cardiovascular system, especially to treat hypertension, to treat angina pectoris, to treat the symptoms of congestive heart failure or to improve kidney function.

More specifically, the compounds of this invention, especially 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride, have proved to be selective peripheral D_2-agonists. For a discussion of various agonist/antagonist activities in the dopaminergic system, one should refer to J. M. Rooyen, et al., S. Afr. Med. J. 59 329 (1981). or I. Cavero et al., Life Sciences, 31 939, 1059 (1982). Otherwise speaking, the main focus of action is at the presynaptic α-dopaminergic receptors which may also be called "D_2-receptors." Activation of the D_2-receptors on the sympathetic nerve terminals inhibits the release of noradrenaline, thereby, promoting vasodilation, among other beneficial cardiovascular actions.

In the perfused rabbit ear artery test [J. P. Hieble et al., Arch. Pharmacol., 309 217 (1979)], 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride had an EC_{50} of 72 nM. It was active in vivo in the dog in both the cardiovaccelerator nerve and perfused hind limb preparations and did not cause tachyphylaxis in the latter preparation as did its 7-hydroxy congener of the prior art. Intravenous infusion of this species of this invention in the DOCA-salt hypertensive and spontaneously hypertensive rats reduced blood pressure and heart rate. A similar but weaker effect on blood pressure and heart rate was observed with the lead compound in the renal hypertensive rat and in the normotensive rat tests. In conscious DOCA salt hypertensive rats, oral doses of 10 mg/kg of the di-n-propylaminoethyl compound demonstrated an anti-hypertensive effect. This species seems more readily absorbed from the gastrointestinal tract than is its 7-hydroxy congener.

The pharmaceutical compositions of this invention which have pharmacodynamic activity within the cardiovascular system, for example renal vasodilatation, correcting hemodynamic imbalance, anti-anginal activity, hypotensive activity and bradycardia, are prepared in conventional dosage unit forms by incorporating a

compound of formula I, or a pharmaceutically acceptable acid addition salt thereof, into a nontoxic pharmaceutical carrier according to accepted pharmacy procedures in a nontoxic quantity sufficient to produce the desired pharmacodynamic activity in a subject, animal or human. Preferably, the compositions will contain the active ingredient in an active but nontoxic quantity selected from the range of about 50 mg to about 500 mg, preferably about 75–250 mg, of active ingredient, as the base, per dosage unit. This quantity depends on the relative potency of the base compound compared with that of the prototypal species, 4-(2-di-n-propylaminoethyl)-2(3H)-indolone, as well as on the specific biological activity desired, the route of administration, that is, whether oral or parenteral, and the condition and size of the patient.

The pharmaceutical carrier employed for the dosage units is, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate or stearic acid. Exemplary of liquid carriers are isotonic saline for parenteral use or syrup, peanut oil, olive oil or water for soft gelatin capsules. Similarly, the carrier or diluent may include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or admixed with a wax. Such sustained release products as well as prodrug derivatives which may be gradually metabolized to the active parent can be employed to prolong the unique biological activity of the compounds of this invention or to attack receptors at a specific location.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier for oral or rectal administration is used, the mixed preparation can be tableted, placed in a hard gelatin capsule in powder or sustained release pellet form, in a suppository or in the form of a troche or lozenge. The amount of solid carrier will vary widely but, preferably, will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampul or an aqueous or nonaqueous liquid suspension for oral administration.

The method of this invention for producing D_2-agonist activity manifests itself by inducing renal vasodilatation, anti-anginal, anti-hypertensive and bradycardic activity. It comprises administering orally, rectally or parenterally to a subject in need of such activity a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, usually combined with a pharmaceutical carrier, in a nontoxic amount sufficient to produce said activity. The route of administration may be any route which effectively transports the active compound to the cardiovascular system receptors which are to be selectively stimulated. Such routes include oral, rectal or parenteral administration, the oral route being preferred. The parenteral administration may be subcutaneous or, preferably, intravenous for critical use.

Advantageously, doses selected from the dosage unit ranges given above will be administered several times, such as from one to five times, a day. The daily dosage regimen is selected from the range of about 50 mg to about 1.0 g, preferably 200–750 mg for oral administration and 50–500 mg for parenteral administration. When the method described above is carried out, D_2-agonist activity is produced.

For an average size human using 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride as an active ingredient, a typical dose to show anti-hypertensive activity would be selected from the range of from about 100–250 mg of base equivalent for each dosage unit which is adapted for oral administration and which is administered orally from 1–4 times daily.

The following examples are designed solely to illustrate the preparation and use of the compounds of this invention. The temperatures are Centigrade. Other variations of these examples will be obvious to those skilled in the art.

EXAMPLE 1

A mixture of 3.44 g (9.63 mmoles) of 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944), 22 cc of dimethylformamide, 1.79 g (9.91 mmoles) of 5-chloro-1-phenyl-1H-tetrazole, 220 cc of acetone, 10 cc of water and 2.90 g (21 mmoles) of anhydrous potassium carbonate was refluxed for about 3 hours at which time thin layer chromatographic analysis (silica gel GF, 75-23-2 ethyl acetate-methanol-conc. ammonium hydroxide) indicated that the reaction was complete.

After cooling the reaction mixture in an ice-bath, the inorganic salts were removed by filtration and washed with acetone. The combined filtrates were concentrated in vacuo. The residual syrup was diluted with saturated brine and extracted with three portions of diethyl ether. The gathered extracts were dried over anhydrous magnesium sulfate, clarified with charcoal and treated with ethereal hydrogen chloride until precipitation was complete. The solid was slurried in diethyl ether and decanted several times, filtered and air-dried to give 3.8 g (86%) of tan 4-(2-di-n-propylaminoethyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone hydrochloride. Recrystallization from 200 cc of hot acetonitrile gave 2.6 g (59%) of microcrystalline product, m.p. 245°–6°. Evaporation of the mother liquor and recrystallization of the residue from 25 cc of hot acetonitrile gave an additional 400 mg of product, m.p. 244°–5°.

A mixture of 2.64 g (5.78 mmoles) of the phenyl tetrazole ether, 200 cc of glacial acetic acid and 1.49 g of 10% palladium-on-carbon was hydrogenated in a Parr apparatus at 50 p.s.i. for 20 hours at 50°. The warm reaction mixture was filtered through glass fiber filter-paper and the catalyst washed thoroughly with hot glacial acetic acid. The filtrate was concentrated in vacuo, the pale yellow waxy residue distributed in water and ethyl acetate. After acidification of the aqueous phase with 3N hydrochloric acid, the organic phase was separated and extracted once with 1N hydrochloric acid. The combined aqueous phases were adjusted to pH 8.5 with aqueous 10% sodium hydroxide and extracted with a mixture of ethyl acetate and diethyl ether. The combined organic extract was back-washed once with saturated brine, dried over anhydrous magnesium sulfate, clarified with charcoal, treated with ethereal hydrogen chloride and evaporated to dryness in vacuo to give 1.64 g (96%) of pale yellow crystalline solid; 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride. Recrystallization from 260 cc of hot acetonitrile which was concentrated to about 50 cc gave 1.26 g (74%) of pale yellow microcrystalline powder, m.p. 240°–242°.

The hydrochloride salt (500 mg) is shaken in the presence of ether/5% sodium carbonate solution. The ether layer is separated, dried and evaporated to give the free base which is used to prepare other salt forms such as the methanesulfonate, ethanedisulfonate, sulfate

or sulfamate by reacting aliquots of the base in ether with an excess of each acid.

EXAMPLE 2

A mixture of 22.0 g (0.105 mole) of 2-methyl-3-nitrophenylacetic acid (V. Askam et al., J. Chem. Soc. (C) 1969 1935) and 25 cc of thionyl chloride was slowly heated to 75° and the copious evolution of gasses allowed to moderate. The temperature was raised and the solution was refluxed for 1 hour. The reaction was concentrated in vacuo. The residual straw-colored syrup was chased several times with dry toluene, diluted with 100 cc of dry toluene and added to a cool (10°) mixture of 13 g of sodium carbonate in 150 cc of water and 150 cc of toluene containing 14.5 cc (10.6 g, 0.12 mole) of di-n-propylamine with very slow stirring. After 30 minutes, the ice-bath was removed. Stirring was continued for one hour. An additional 0.5 g of solid sodium carbonate was added to the reaction. After 15 minutes, the organic phase was separated, washed with 5% aqueous sodium carbonate followed by 2N hydrochloric acid and, finally water. The organic solution was dried over magnesium sulfate, concentrated in vacuo and pumped free of solvent to give 29.5 g of 2-methyl-3-nitrophenyl-N,N-di-n-propyl acetamide as a straw-colored syrup.

The total syrup (105 mmoles) was taken up in 250 cc of anhydrous tetrahydrofuran and treated with 160 cc of 1.0 M borane in tetrahydrofuran at room temperature for 1 hour. The reaction was refluxed for 2 hours, then cooled. Excess reagent was destroyed by the cautious addition of dry methanol. This solution was concentrated in vacuo. The residual syrup was treated with 40 cc of 6N hydrochloric acid for 1 hour on the steam-bath, cooled, basified with 40% sodium hydroxide and extracted with 3 portions of ether. The combined organic phase was washed once with brine, concentrated in vacuo and distilled in a Kugelrohr apparatus at 115°–118°/0.1 mm Hg to give 21.6 g of a mobile yellow oil; 2-methyl-3-nitrophenylethyl-N,N-di-n-propyl amine.

To a solution of 2.38 g (0.103 gram atoms) of sodium metal in 52 cc of absolute ethanol at room temperature was added 18.51 g (0.07 mole) of the nitro compound in one portion, with stirring, followed by 15.42 g (0.103 mole) of diethyl oxalate. The reaction was refluxed under nitrogen for about 20 minutes, cooled, quenched on 700 cc of ice-water and acidified with 3N hydrochloric acid. This aqueous solution was washed with a small volume of ether, basified to pH 8.5 with solid sodium carbonate and extracted with 3 portions of ether. The combined ether extract was washed with saturated brine, dried over anhydrous magnesium sulfate, clarified with charcoal and concentrated in vacuo. The residue was triturated with cold petroleum ether, filtered and air-dried to give 6.0 g of ethyl 6-(2-di-n-propylaminoethyl)-2-nitrophenylpyruvate as a yellow powder. The triturate was concentrated in vacuo and distilled to give 7.3 g of recovered starting material which was recycled. In the same manner, a total of three recycles provided 11.0 g of ethyl-6-(2-di-n-propylaminoethyl)-2-nitrophenylpyruvate.

A cold (10°) solution of 10.24 g (28.1 mmoles) of the pyruvate in 196 cc of 2% sodium hydroxide was treated with 5.0 cc of 30% hydrogen peroxide dropwise over several minutes. The cooling bath was removed and stirring was continued for 1.5 hours during which time the reaction became much lighter in color. A small amount of insoluble material was removed by filtration. The pH was adjusted to 1.5 by the cautious addition (foaming) of about 12 cc of conc. hydrochloric acid. This solution was concentrated in vacuo at 45°, reconstituted with water and evaporated twice more. The residue was slurried in a minimum volume of dilute hydrochloric acid, filtered and air-dried to give 6.40 g of 2-nitro-6(2-di-n-propylaminoethyl)-phenyl acetic acid hydrochloride as a white powder.

A mixture of 5.83 g (16.9 mmoles) of 2-nitro-6-(2-di-n-propylaminoethyl)-phenyl acetic acid hydrochloride and 0.6 g of 5% palladium-on-carbon in 250 cc of ethanol was hydrogenated at 50 p.s.i. over 5.5 hours. The catalyst was filtered, washed with ethanol, and the filtrate evaporated to dryness in vacuo. The white residue was crystallized from 550 cc of hot acetonitrile to give 3.89 g of 4-(2-di-n-propylaminoethyl)-2(3H)indolone hydrochloride, mp 240°–2°.

Anal. Calcd. for $C_{16}H_{24}N_2O$ HCl: C, 64.74; H, 8.49; N, 9.44. Found: C, 64.82; H, 8.26; N, 9.28.

EXAMPLE 3

A mixture of 2.73 g (10.0 mmoles) of 4-(2-aminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944), 200 cc of dimethylformamide, 1.86 g (10.3 mmoles) of 5-chloro-1-phenyl-1H-tetrazole, 10 cc of water and 2.9 g (21 mmoles) of anhydrous potassium carbonate is stirred at room temperature for 2 days or until thin layer analysis indicates that no starting material remains. The reaction is filtered and the filtrate is acidified with dil. hydrochloric acid, concentrated in vacuo and the residue triturated with abs. ethanol. The triturate is clarified with charcoal and evaporated to dryness in vacuo. The hydrochloride salt of 4-(2-aminoethyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone is hydrogenated directly in 200 cc of glacial acetic acid using 50% by substrate weight of 10% palladium-on-carbon at 50 p.s.i. for 20 hours at 50°. The warm reaction mixture is filtered. The catalyst is washed thoroughly with hot acetic acid. After the filtrate is concentrated in vacuo, the residue is stripped several times from dilute hydrochloric acid and crystallized from ethanol to give 4-(2-aminoethyl)-2(3H)-indolone hydrochloride.

EXAMPLE 4

A mixture of 0.5 g of 4-(2-aminoethyl)-2(3H)-indolone hydrochloride, prepared as in Example 3, 2.2 g of isobutyraldehyde, 0.3 g of 5% palladium-on-charcoal and 75 ml of glacial acetic acid is hydrogenated at 55 p.s.i. of hydrogen for 5 hours. The catalyst is separated by filtration and washed with acetic acid. The combined mother liquor-washings is evaporated in vacuo to give a residue which is taken up in cold methanol and treated with methanolic hydrogen bromide to give, upon concentration and cooling; 4-(2-di-isobutylaminoethyl)-2(3H)-indolone hydrobromide.

EXAMPLE 5

A mixture of 0.9 g of 4-(2-aminoethyl)-2(3H)-indolone, 0.23 g of 4-benzyloxyphenylacetaldehyde, 0.25 g of 10% palladium-on-charcoal and 100 ml of ethanol is hydrogenated at 50 p.s.i. at 50° until the uptake of hydrogen is complete. After filtration, the mother liquors are evaporated to give 4-[2(4-hydroxyphenethylamino)-ethyl]-2(3H)-indolone as the residue. This base in alcohol is treated with an excess of methylsulfonic acid to give the methylsulfonate salt.

Repeating this reaction with 4-n-propylaminoethyl-7-hydroxy-2(3H)-indolone and butyraldehyde gives 4-n-butyl-n-propylamino-ethyl-7-hydroxy-2(3H)-indolone hydrochloride.

EXAMPLE 6

Substituting 2.2 g of 4-(3-dimethylaminopropyl)-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) for 4-(2-di-n-propylaminoethyl)-7-hydroxy-2(3H)-indolone hydrobromide in Example 1 gives 4-(3-dimethylaminopropyl)-7-(1-phenyl-1H-tetrazol-5-yloxy)-2(3H)-indolone hydrochloride and, then, 4-(3-dimethylaminopropyl)-2(3H)-indolone base as well as the ethanedisulfonate salt as described above.

Substituting 4-n-propylaminoethyl-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) gives 4-n-propylaminoethyl-2-(3H)-indolone hydrochloride.

Substituting 4-dimethylaminopropyl-7-hydroxy-2(3H)-indolone hydrobromide (U.S. Pat. No. 4,314,944) gives 4-dimethylaminopropyl-2(3H)-indolone hydrochloride.

EXAMPLE 7

4-Aminoethyl-2(3H)-indolone (10 g) is reacted with two mole equivalents of allyl bromide and 4 equivalents of triethylamine in acetonitrile with mild heat for several hours. The reaction mixture is evaporated. The residue is suspended in water. The mixture is extracted with ethyl acetate. The extracts are washed, dried and evaporated to give 4-di-allylaminoethyl-2(3H)-indolone. This material (1 g) is dissolved in ether-ethanol and treated with methane sulfonic acid to give the methane sulfonate salt. Using benzyl bromide gives 4-dibenzylaminoethyl-2(3H)-indolone.

EXAMPLE 8

Anhydrous tetrahydrofuran (10 cc) at 20° under nitrogen was treated with 2.0 cc (4.8 mm) of 2.4 M n-butyl lithium in hexane followed by 0.49 g (1.5 mm) of 4-di-n-propylaminoethyl-7-methoxy-2(3H)-indolone hydrochloride and 0.349 g (3 mm) of N,N,N',N'-tetramethylethylene diamine. Gas evolution and dissolution of the salt was observed.

The reaction mixture was cooled in a dry ice-propanol bath and treated with 1.5 mm of iodomethane in one portion. After stirring in the cold for 10 minutes, the bath was removed and stirring continued for 2 hours. The mixture was quenched in 20 cc of saturated ammonium chloride solution, diluted with ethyl ether. The organic layer was separated. The remaining material was again extracted twice. The combined dried extracts were concentrated in vacuo, stripped from ethyl ether and carbon tetrachloride.

Analysis of the solid demonstrated a mixture of 10% starting material and a 50—50 mixture of di- and mono 3-methylated product. The mixture was realkylated to give 169 mg of 3,3-dimethyl-4-di-n-propylaminoethyl-7-methoxy-2(3H)-indolone.

This material is hydrolyzed as described in U.S. Pat. No. 4,314,944, Example 4 then, dehydroxylated in the form of the crude product as described above to give 3,3-dimethyl-4-di-n-propylaminoethyl-2(3H)-indolone hydrochloride.

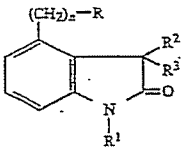
The Kende process was repeated using the same quantities but using 0.61 cc (9.8 mm) of methyl iodide at −70°. The mixture was allowed to warm to −25° and held there for 1 hour followed by 3 hours at room temperature. After working up as described, 4-di-n-propylaminoethyl-7-methoxy-3-methyl-2(3H)-indolone was recovered. This is treated with boron tribromide and, then, 5-chloro-1-phenyl-1H-tetrazole to give 4-di-n-propylaminoethyl-3-methyl-2(3H)-indolone hydrochloride.

EXAMPLE 9

4-(2-di-n-Propylaminoethyl)-2(3H)-indolone hydrochloride (125 mg) is mixed with 200 mg of lactose and 2 mg of magnesium stearate, filled into a hard gelatin capsule and administered to a hypertensive patient from 1–3 times daily.

What is claimed is:

1. A compound of the structural formula:



in which:

R is amino, C_{1-6}-lower alkylamino, di-(C_{1-6}-lower alkyl)amino, allylamino, diallylamino, N-(C_{1-6}-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl)amino, and

R^1, R^2 and R^3 are, each, hydrogen or C_{1-6}-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

2. The compound of claim 1 in which R^1, R^2 and R^3 are hydrogen, n is 2 and R is amino, di-n-propylamino, n-propyl-n-butylamino or 4-hydroxyphenethylamino.

3. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

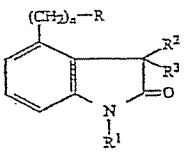
4. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone as the free base.

5. The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.

6. The compound of claim 1 being 4-(2-aminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

7. The compound of claim 1 being 4-(4-hydroxyphenethylaminoethyl-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

8. A pharmaceutical composition having D_2 receptor agonist activity comprising a nontoxic, agonist quantity of a compound of the structural formula:



in which:

R is amino, C_{1-6}-lower alkylamino, di-(C_{1-6}-lower alkyl)amino, allylamino, diallylamino, N-(C_{1-6}-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-

hydroxyphenethylamino or di-(4-hydroxyphenethyl)amino, and

R^1, R^2 and R^3 are each hydrogen or C_{1-4}-lower alkyl; or a pharmaceutically acceptable acid addition salt thereof, in dosage unit form, combined with a pharmaceutical carrier.

9. The composition of claim 8 in which the D_2-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or a pharmaceutically acceptable, acid addition salt thereof.

10. The composition of claim 8 in which the D_2-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride.

11. The composition of claim 8 in dosage unit form adapted for use as an antihypertensive composition.

12. The composition of claim 8 in which the quantity per dosage unit is selected from the range of 50–500 mg base weight of said compound.

* * * * *

EXHIBIT C

United States Patent [19]

Owen

[11] Patent Number: 4,824,860

[45] Date of Patent: Apr. 25, 1989

[54] TREATMENT OF PARKINSONS DISEASE

[75] Inventor: David A. A. Owen, Welwyn Garden City, England

[73] Assignee: Smith Kline & French Laboratories Limited, Welwyn Garden City, England

[21] Appl. No.: 196,653

[22] Filed: May 19, 1988

[30] Foreign Application Priority Data

May 21, 1987 [GB] United Kingdom 8712073

[51] Int. Cl.[4] A61K 31/40

[52] U.S. Cl. 514/418

[58] Field of Search 514/418

[56] References Cited

U.S. PATENT DOCUMENTS

4,452,808 6/1984 Gallagher 548/486

4,588,740 5/1986 Gallagher 548/486

FOREIGN PATENT DOCUMENTS

113964 10/1986 European Pat. Off. .

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Chem. Abst.—105, (1986)—152924D.

Gallagher et al., *J. Med. Chem. 28:1533, (1985).*

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Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Stuart R. Suter; Alan D. Lourie

[57] ABSTRACT

The present invention relates to the use of certain indolone derivatives in particular, 4-(2-di-n-propyl-aminoethyl)-2-(3H)-indolone in a method of treatment of Parkinsons disease.

3 Claims, No Drawings

TREATMENT OF PARKINSONS DISEASE

The present invention relates to a method of treatment of disorders of the central nervous system, in particular Parkinsons Disease, by the administration of certain indolone derivatives.

Parkinsons Disease is a disturbance of voluntary movement in which muscles become stiff and sluggish, movement becomes clumsy and difficult and uncontrollable rhythmic twitching of groups of muscles produces characteristic shaking or tremor. The condition is believed to be caused by a degeneration of pre-synaptic dopaminergic neurones in the brain. The absence of adequate release of the chemical transmitter dopamine during neuronal activity thereby leads to the Parkinsonian symptomatology.

Currently, the most widely used treatment for Parkinsonism is administration of L-DOPA, a precursor of dopamine which acts indirectly by replacing the missing dopamine. However, disadvantages are associated with the use of L-DOPA, for example, patients often suffer from side-effects such as dyskinesia and on-off effects, and it is necessary to administer L-DOPA in conjunction with a peripheral dopa-decarboxylase inhibitor such as carbidopa or benzaseride. These inhibitors prevent the peripheral degradation of levodopa to dopamine, thus enabling more drug to enter the brain and limiting peripheral side-effects. Such treatment improves quality of life for patients but does not halt disease progression. Furthermore, such treatment is associated with a number of adverse effects including nausea, vomiting, abdominal distension and psychiatric side-effects (for example, toxic confusional states, paranoia and hallucinations).

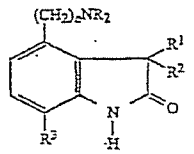
An alternative form of therapy is to administer post-synaptic dopamine agonists, for example ergot alkaloids such as bromocriptine—however, this approach is also associated with side-effects. For example, patients receiving bromocriptine often experience dyskinesia psychiatric problems, and in a small number of cases experience vasopastic phenomena and angina. In addition bromocriptine also causes psychiatric side-effects such as hallucinations.

In view of the foregoing, it is clear that there is a continuing need for the provision of effective safe medicaments for the treatment of Parkinsonism.

It has now been found that certain indolone derivatives known in the art as pre-synaptic D_2-agonists having utility as cardiovascular agents (see EP No. 113964-B), also are post-synaptic D_2 -agonists in the brain and hence are expected to have utility in the treatment of Parkinsonism.

This finding is particularly interesting since such compounds have previously been reported as not being capable of producing the central behavioural effects often seen with dopamine agonists (see Gallagher, G., Jr. et al., J. Med. Chem. 1985, 28 1533–1536). In addition, the compounds of the present invention show distinct unexpected advantages over known dopamine agonists in having been found to have additional effects on the central nervous system; namely, anti-depressant and anxiolytic effects. Furthermore, preclinical studies appear to indicate that the compounds show minimal liability to cause dyskinesia. In particular the anti-depressant and anxiolytic effects of the compounds of the present invention are perceived to be advantageous as patients receiving current therapies often also need to take separate anti-depressant medication. The presence of such qualities in a single compound may therefore reduce the need for such separate therapy.

The present invention therefore provides a method of treatment of Parkinsons Disease which comprises administering an effective non-toxic amount of a compound of structure (I)



(I)

in which

each group R is hydrogen or C_{1-4}alkyl;

R^1 and R^2 are each hydrogen or C_{1-4}alkyl;

R^3 is hydrogen or hydroxy; and

n is 1 to 3;

or a pharmaceutically acceptable salt thereof to a subject in need thereof.

Preferably, both groups R are C_{1-4}alkyl in particular propyl and R^1 and R^2 are both hydrogen.

Suitably R^3 is hydroxy; preferably R^3 is hydrogen.

In particular preferred compounds for use in the method of the present invention include the compound of structure (I) in which both groups R are propyl, R^1, R^2 and R^3 are hydrogen and n is 2 namely, 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone or a pharmaceutically acceptable salt thereof.

Suitable salts will be apparent to those skilled in the art and include, for example acid addition salts, preferably the hydrochloride.

The compounds of structure (I) and their pharmaceutically acceptable salts can be prepared by the methods described in U.S. Pat. No. 4,452,808.

In therapeutic use for the treatment of Parkinsonism, the compounds are incorporated into standard pharmaceutical compositions. They can be administered orally, parenterally, rectally or transdermally.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when administered parenterally (i.e. by injection or infusion) can be formulated as solutions or suspensions.

A composition for parenteral administration will generally consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository composition comprises a compound of structure (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

A typical transdermal formulation comprises a conventional aqueous or non-aqueous vehicle, for example, a cream, ointment lotion or paste or in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dose form. Each dosage unit for oral administration contains preferably from 1 to 50 mg (and for parenteral administration contains preferably from 0.1 to 15 mg) of a compound of structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 100 mg, preferably between 1 mg and 50 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 50 mg, preferably between 0.1 mg and 15 mg, of the compound of structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy.

BIOLOGICAL DATA

Using the compound 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride (Compound A, prepared according to procedures described in European Patent No. 113964-B) the following tests were performed:

1. Mouse spontaneous locomotor activity using individual cages equipped with photocells.
2. Mouse spontaneous locomotor activity using treadwheels.
3. Mouse spontaneous locomotor activity measuring climbing frame behaviour.
4. Measurement of stereotyped behaviour in the mouse.
5. Rat spontaneous locomotor activity using individual cages equipped with photocells: measurement of stereotypy.
6. Measurement of hyperactivity following direct administration into the mesolimbic nucleus accumbens of the rat. An indicator of anti-depressant activity.
7. Effect on observed locomotor activity following direct administration into the extrapyramidal caudate-putamen (striatum). A test for anti-Parkinsonism potential.
8. Measurement of anti-depressant activity in the mouse using the 'Porsolt Test'.
9. Anxiolytic activity in the mouse using a black and white test box.
10. MPTP-treated marmoset model. A test for anti-Parkinson activity.

A. Effect of Compound A on Spontaneous Locomotor Activity in Mice

Compound A caused inhibition of spontaneous locomotor activity in the mouse in each of the first three tests at doses of 1.0 and 10.0 mg/kg i.p. Statistically significant inhibition ($P<0.01$—0.001) was measured following 10 mg/kg in test No. 1 and 1.0 mg/kg in test No. 3.

Stimulation of locomotor activity, at a statistically significant levels ($P<0.001$), was seen after 100 mg/kg Compound A in the photocell and treadwheel tests, but not in the climbing test where the original inhibition was reversed. This biphasic activity, also exhibited by amphetamine and apomorphine in these tests, is consistent with that of a dopamine agonist having ability to stimulate presynaptic (autoreceptors) at low doses and post-synaptic receptors at a high dose. (Amphetamine is a known mood enhancer and apomorphine is a standard D_2 agonist of the same pharmacological class as compound A). These tests are considered to indicate dopamine agonist activity in both extrapyramidal and limbic systems.

B. Ability of Compound A to Induce Stereotypy in Rats or Mice

At doses of 1.0, 10.0 and 100 mg/kg i.p. Compound A caused no dose dependent stereotypies in the mouse or rat (tests 4 and 5). Amphetamine, at doses up to 10.0 mg/kg i.p. and apomorphine, 2.0 mg/kg s.c., produced marked stereotyped behaviour such as continuous biting, gnawing and licking in both species whereas Compound A only caused periodic sniffing.

Results

In these two tests Compound A shows a different profile to other known dopamine agonists suggesting a more selective mode of action.

C. Effect of Compound A on Locomotor Activity in the Rat

Doses of 10.0 and 100.0 mg/kg i.p. Compound A caused statistically significant ($P<0.001$), dose-related increases in spontaneous locomotion (test 5) which lasted, at the higher dose, in excess of 2.5 hours. Enhancement of locomotor activity by amphetamine and other dopamine agonists is difficult to measure because it is complicated by the development of stereotypies. When injected directly into the mesolimbic nucleus accumbens via an indwelling cannula (test 6), Compound A (10 μg) caused a marked ($P<0.001$) increase in spontaneous locomotion. Amphetamine, at the same dose, was equally effective, but the lower dose of Compound A (1.0 μg) was ineffective, causing a tendency to inhibition, especially during the first 10 minutes after dosing. Direct action of a compound to cause hyperactivity following administration into the mesolimbic nucleus accumbens is considered to be indicative of anti-depressant activity.

In a separate experiment, designed to measure stimulation of the striatum by recording asymmetry and circling behaviour, Compound A (0.01–10.0 μg), apomorphine (up to 50 μg) or amphetamine (up to 100 μg) were administered, unilaterally, via an indwelling cannula into the extrapyramidal caudate-putamen (test 7). Apomorphine and amphetamine were both inactive in this test but Compound A caused marked contralateral

asymmetry and circling behaviour which became statistically significant at 1.0 and 10.0 μg.

Conclusion

The results from this test suggest an indication for anti-Parkinson potential for this compound.

D. Anti-Depressant Activity Using the 'Porsolt Test'

Compound A, at 0.1–10 mg/kg i/p., showed statistically significant ($P<0.05$) anti-depressant activity in mice using the Porsolt test, a test measuring the animals ability to keep stable in water. The activity was similar to that of (+) amphetamine (0.625–2.5 mg/kg i.p.) and greater than amitriptyline (2.4–40 mg/kg i.p.). The known anti-Parkinson agent Bromocriptine, 0.1–1 mg/kg i.p. caused a statistically significant reduction in swimming time at the higher dose.

Conclusion

Contrary to the effect seen in this test with the known anti-Parkinson agent bromocriptine, a compound A was found to exhibit statistically significant anti-depressant activity.

E. Anxiolytic Effect of Compound A

In a study to investigate anxiolytic acitivity in a 'Black and White' test box (test 9), Compound A (0.1–10 mg/kg i.p.) caused a statistically significant increase in the time spent in the white section and a correspondingly reduced period in the black area. This behaviour was similar to that caused by diazepam (0.125–5 mg/kg i.p.) and is consistent with other compounds having clinical anxiolytic activity. In a similar, though separate, study bromocriptine (0.1–1 mg/kg i.p.) caused a statistically significant increase in investigatory activity in the *black* area with no change in the light aversion.

Conclusion

Contrary to the effect seen in this test with the known anti-Parkinson agent bromocriptine, compound A was found to exhibit statistically significant differences in its anxiolytic effect.

F. Anti-Parkinson Activity: MPTP-Treated Marmoset Model

(i) Parkinsonism-like motor deficits (hypokinesia and bradykinesia) were induced in marmosets by the intranigral infusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) for 13 days via an implanted injection unit and osmotic minipump (Test 10). Motor deficits appeared within 3–4 days and persisted for several weeks. Drug assessments were begun after 7–10 days of infusion.

Results

Compound A (0.05–1.0 mg/kg s.c.) fully restored normal motor behaviour, although at 0.05 mg/kg, 1 or 2 marmosets did not respond.

Behavioural measure	Control	MPTP + vehicle	Compound A (mg/kg s.c.) 0.01	0.05	0.1	1.0
LMA (% control)	100	15	26	47*(70)	93**	103**
% time spent in LMA	30	3	4	12*(25)	29**	28**
% time in head movements	85	23	25	36*(80)	85**	84**

LMA—Locomotor activity (movements between perch and cage floor).

Values are means (n=4); S.E.M. <13.6%, except at 0.05 mg/kg, where 1 or 2 animals did not improve (S.E.M. up to 24.2%). Values in parentheses are means from those animals responding.

Significant antagonism of MPTP impairment * $P<0.05$, ** $P<0.01$.

The most marked effect of Compound A was the full restoration of normal movements in the limbs, trunk, head and neck. In particular, characteristic rapid side to side head movements returned, as did normal facial expressions and the motor coordination for complex tasks such as jumping and playing. Furthermore, there was no development of tolerance during dosing (0.1, 1.0 mg/kg s.c.) twice daily for 7 days.

For comparative purposes tests were carried out with two known anti-Parkinson agents L-DOPA and Bromocriptine.

Treatment with L-DOPA (12.5 mg/kg i.p. 30 min. pretreatment) after benserazide (12.5 mg/kg s.c. 90 min. pretreatment) also restored MPTP-induced motor deficits, but at these relatively high doses appeared to be less effective than 0.1 mg/kg s.c. Compound A. Treatment with Bromocriptine (0.1 mg/kg s.c.) had little effect.

Conclusion

The results of this specific test confirm the potential of compound A for use as an anti-Parkinson agent.

(ii) Compound A was administered orally to MPTP treated marmosets at doses of 0.1, 0.5 or 1.0 mg/kg.

Partial reversal of the following MPTP-induced motor deficits were recorded following each dose: percentage time spent in locomotor activity, reduction in speed of head movement, reduction in speed of locomotor activity, lack of interest in surroundings, lack of facial expression, head elevation and percentage time spent in head movement. The response for the lowest dose (0.1 mg/kg, n=2) was submaximal and the highest dose (1.0 mg/kg, n=3) was supramaximal. No emesis occurred at the two lower doses.

Conclusion

The results of this specific test confirm the potential of compound A for use as an anti-Parkinson agent.

G. Receptor Binding Studies

Receptor binding studies, using rat brain, indicated that both bromocriptine and pergolide showed affinity for $5HT_1$ and $5HT_2$ receptors and pergolide also bound to dopamine D_1 receptors. Compound A showed no affinity for any of these receptor subtypes.

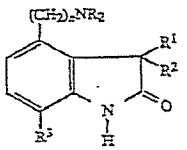
Conclusion

These studies indicate that Compound A is more selective in its binding to receptors than the other D_2-agonists (bromocriptine and pergolide) studied.

I claim:

1. A method of treatment of Parkinsons Disease which comprises administering an effective non-toxic

amount for the treatment of Parkinsons Disease of a compound of the following structure:



in which

each group R is hydrogen or C_{1-4}alkyl;

R^1 and R^2 are each hydrogen or C_{1-4}alkyl;

R^3 is hydrogen or hydroxy; and

n is 1 to 3;

or a pharmaceutically acceptable salt thereof to a subject in need thereof.

2. A method of treatment of Parkinsons Disease which comprises administering an effective non-toxic amount for the treatment of Parkinsons Disease of 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone to a subject in need thereof.

3. A method of treatment of Parkinsons Disease which comprises administering an effective non-toxic amount for the treatment of Parkinsons Disease of 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride to a subject in need thereof.

* * * * *

REDACTED

EXHIBIT D

REDACTED

EXHIBIT E

SKB 14136

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:
my residence, post office address and citizenship are as stated below next to my name;
I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the invention entitled:

"4-AMINOALKYL-2(3H)-INDOLONES"

described and claimed in the attached specification, that I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to this application; that I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns.

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

William H. Edgerton	Registration No. 18,864
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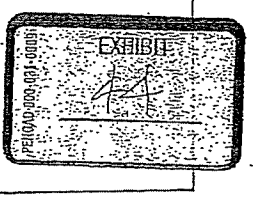
Address all correspondence and telephone calls to William H. Edgerton, P.O. Box 7929, Philadelphia, Pennsylvania 19101, whose telephone number is 215-751-5180.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



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